Dynamic Modeling of Cost-effectiveness of Rotavirus Vaccination, Kazakhstan

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The government of Kazakhstan, a middle-income country in Central Asia, is considering the introduction of rotavirus vaccination into its national immunization program. We performed a cost-effectiveness analysis of rotavirus vaccination spanning 20 years by using a synthesis of dynamic transmission models accounting for herd protection. We found that a vaccination program with 90% coverage would prevent ≈880 rotavirus deaths and save an average of 54,784 life-years for children <5 years of age. Indirect protection accounted for 40% and 60% reduction in severe and mild rotavirus gastroenteritis, respectively. Cost per life year gained was US $18,044 from a societal perspective and US $23,892 from a health care perspective. Comparing the 2 key parameters of cost-effectiveness, mortality rates and vaccine cost at <US $2.78 per dose, vaccination program costs would be entirely offset. To further evaluate efficacy of a vaccine program, benefits of indirect protection conferred by vaccination warrant further study.

Rotavirus is the leading cause of severe acute gastroenteritis in children worldwide (*1*). Rotavirus vaccines Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Rotateq (Merck & Co., Whitehouse Station, NJ, USA) are in use in the national immunization programs in Australia, the United States, Latin America, and a few European countries. In these high- and middle-income countries, rotavirus effects have decreased markedly after introduction of the vaccine (*2–4*). Universal rotavirus vaccination has not been widely implemented in Asia, and the health effects of rotavirus differ considerably across the continent, with the highest mortality rates concentrated in developing areas. In Central Asia, there are also large variations in the reported rotavirus effects by country (*5*), emphasizing the need for local data to guide the decision on the introduction of the vaccine.

Kazakhstan is the most prosperous country in Central Asia. It has a population of 16 million (*6*) and a land mass equal to approximately half of the continental United States. Kazakhstan has large reservoirs of oil and natural gas and is classified as an upper-middle income economy; its gross national income was US $8,220 per capita in 2011 (*7*), making the country ineligible for international funds to introduce new vaccines. Vaccines included in the national childhood immunization program are fully funded by the government. The health effects of rotavirus in Kazakhstan were estimated at 68 deaths, 4,007 hospitalizations, and 32,500 outpatient visits during 2009 (*5*); another study estimated the total annual cost of rotavirus disease to be US $37.5 million (*8*). No current cost-effectiveness analyses of rotavirus vaccines were available for Kazakhstan.

Recently, 2 economic evaluations of the rotavirus vaccination were conducted in low-income countries in Central Asia (*9*,*10*), but because of differences in rotavirus epidemiology, health care costs, and economy, the results are not generalizable to Kazakhstan. These studies were performed on the basis of static models, which implicitly assume that the probability for disease exposure is constant in time. In contrast, immunization will not only reduce the probability of a vaccinated child to become ill but will also lower the exposure of the virus to others (i.e., herd protection).

Models that account for changes in transmission over time are referred to as dynamic models. Cost-effectiveness studies of rotavirus vaccination performed on the basis of dynamic transmission modeling were recently used in the United States (*11*), England, and Wales (*12*). To the best of our knowledge, this approach has not been applied in middle-income countries or in settings with a transitional economy. These countries face particular challenges because they are not eligible for international financing

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of vaccines, and their resources for new health interventions are limited. Rotavirus vaccine effectiveness has been shown to correlate with income level within a country (*13*). It is possible that rotavirus vaccines may perform worse in middle-income settings than in upper-income countries. Hence, scientifically sound estimates of the effect of rotavirus vaccination are in demand.

We present a cost-effectiveness study of rotavirus vaccination in a middle-income country using dynamic modeling. We incorporated direct effects such as death rates and indirect effects such as herd protection of a nationwide vaccination program. Our purpose for the study is twofold: to inform the impending decision on the introduction of rotavirus vaccination into the national immunization program in Kazakhstan, and to compare the cost-effectiveness of a rotavirus vaccination program in a middle-income country with that reported for high-income settings.

Materials and Methods

We adapted our previously published dynamic model for rotavirus (*14*,*15*) to Kazakhstan. The model is presented in the online Technical Appendix (wwwnc.cdc.gov/EID/article/20/1/13-0019-Techapp1.pdf).

Vaccination Parameters

We modeled the effect of introducing the 2-dose rotavirus vaccine Rotarix in the childhood immunization program in Kazakhstan. We implemented vaccination in the model assuming that the vaccine was effective from the first dose at 2 months, similar to other modeling studies (*15*). We chose a 2-dose rotavirus vaccine versus a 3-dose product because it may be more feasible in practice to achieve high coverage for a vaccine requiring fewer doses. Rotarix demonstrated 96% efficacy against rotavirus gastroenteritis (RVGE) hospitalizations in clinical trials and 90% field effectiveness against hospital admissions in high-income European countries (*26*). A lower field effectiveness range of 76%–79% was reported from the middle-income countries in Latin America (*26*–*28*). Because of lack of clinical trials of rotavirus vaccines in countries like Kazakhstan that are in transitional economies, it is difficult to predict the vaccine performance in these settings. On the basis of the aforementioned findings and our own assumptions, we applied a vaccine efficacy of 80% (range 72%–86%) against severe RVGE and 58% (range 51%–64%) against mild RVGE. The vaccine efficacies were varied by varying the proportions of RVGE infection, and severe RVGE infection in vaccinated children (online Technical Appendix). We did not adjust the vaccine efficacy for specific rotavirus genotypes because the strains circulating in Kazakhstan are globally common (*29*). Pre- and post-licensure data from developing settings indicate that vaccine protection may wane in the second year of life (*30*,*31*). We conservatively assumed vaccine protection to be 1 year, commencing after administration of the last dose at 4 months of age; that is, children were assumed to be fully protected on average until 16 months of age. However, studies from industrialized settings demonstrated high vaccine efficacy through 3 years of life (*32*,*33*). Therefore, we increased duration of vaccine protection to 2 years in a separate scenario analysis.

The vaccination program in our model was hypothetically initiated on January 1, 2012, with a linear buildup of vaccine coverage during the first 6 months. After this period, the vaccination coverage was assumed to be constant at a fixed level. In Kazakhstan, rotavirus vaccine would be administered concomitantly with the diphtheria–tetanus toxoid–pertussis (DTP) vaccine. The reported coverage for 3 doses of DTP in Kazakhstan is 99% (*7*), although a recent study suggests that only 76% of children 12–60 months of age receive all 3 doses of the DTP vaccine without delay (*34*). Considering age restrictions for the administration of rotavirus vaccines, coverage for the rotavirus vaccine may be lower than for other traditional vaccines administered under the World Health Assembly Expanded Programme on Immunization (*35*) because vaccination may not always be on time. We therefore applied 90% coverage in the base case, but varied coverage between 80% and 100% to explore the effect of this parameter on the cost-effectiveness of vaccination. Similarly to other studies, we did not consider an increased risk for intussusception or any other adverse events after rotavirus vaccination (*2*).

Disease Outcomes

We calculated the numbers of rotavirus-associated deaths, hospitalizations and outpatient visits in children <5 years from the modeled incidence of severe RVGE (I_s). We assumed that all children with severe RVGE require outpatient care or hospital care, and on the basis of local data, we modeled that 80% of children who were hospitalized with acute diarrhea sought medical care before admission (*8*). We calculated the numbers of rotavirus homecare episodes (without health care encounters) from the modeled incidence of mild RVGE (I_m), whereas the number of rotavirus-associated deaths and hospitalizations was calibrated to the 2009 estimates of 68 (95% CI 63–74) deaths and 4,007 (95% CI 3,740–4,274) hospitalizations based on a recent study from Kazakhstan (*8*) (online Technical Appendix).

Model Uncertainty and Scenario Analyses

We considered uncertainty related to natural history parameters (Table 1), model calibration, and vaccine efficacy and uptake. The role of adults in rotavirus transmission is a key uncertain factor (*15*). Because no sentinel data in this age group were available, we varied the infectiousness of later rotavirus infections relative to that of the primary infection between 1/5 and 1/10 (*14*,*15*). We also

Table 1. Natural history and vaccine-related parameters used in dynamic modeling of cost-effectiveness of rotavirus vaccination, Kazakhstan

Parameter	Base value [range]	Reference/source
Demographic		
Population during 1980	15,926 million	(*16*)
Birth cohort*	[217,580–367,750]	(*16*,*17*)
Mortality rate in <1 y*	20–54 per 1,000 births	(*16*,*17*)
Mortality rate in 1–4 y*	3.9–6.3 per 1,000 births	(*16*,*17*)
Net yearly migration rate*	−18.6–0.1 per 1,000	(*16*,*17*)
Deaths per year*	[128,570–180,000]	(*16*,*17*)
Natural history		
Duration of maternal protection	70 d	(*18*)
Duration of latency period	0.5 d	(*19*)
Infectious period (days)	8 (first); 6 (second); 4 (later)	(*20*–*22*)
Relative susceptibility	1 (first); 0.62 (second); 0.40 (later)	(*23*)
Relative infectiousness	1 (first); 0.5 (second); [0.1–0.2] (later)	Author assumption
Proportion of infections with RVGE	0.47(first); 0.25 (second); 0.24 (later)	(*23*)
Severe RVGE	0.13 (first); 0.04 (second); 0 (later)	(*23*)
Duration of complete immunity	[6–12 mo]	(*24*)
Vaccination		
Sero-conversion rate	0.96	(*25*)
Relative infectiousness†	0.5	Assumption
Relative susceptibility†	0.62	Author assumption
Prop. of infections with RVGE	0.30 [0.25–0.35]	(*25*–*27*)
Severe RVGE	0.1175 [0.0885–0.139]	(*25*–*27*)
Coverage	0.9 [0.8–1.0]	Author assumption
Duration of complete immunity	12–24 mo]	Author assumption
Fitted‡		
Infectivity parameter, $\beta 0$	1.889–2.605	Author calculation
Seasonal forcing, $\beta 1$	0.025–0.046	Author calculation
Phase angle, θ	0.011–0.251	Author calculation
Mixing (relative susceptibility)§ 0–7m, 8–23 m, 24–35 m	1.077–2.765	Author calculation

*Demographic parameters vary over the time period 1980-2031; only minimum and maximum values are listed in the table. All simulations are performed using the same set of demographic parameters.
†Vaccine efficacy calculated for children with no previous natural infection.
‡Details on the fitted parameters of the five candidate models; see corresponding model fits in online Technical Appendix Table wwwnc.cdc.gov/eid/article/20/1/13-0019-Techapp1.pdf; seasonal forcing: $\beta 0(1 + \beta 1)\sin(2\pi t / 365 + 0)$.
§Relative susceptibility in children <3 years (online Technical Appendix, section 1).

varied the mean duration of complete immunity after rotavirus infection from 6 to 12 months. All models were scored according to how well they fit with the sentinel data, adopting a likelihood-based approach by using the Akaike information criterion. In total, 5 candidate models (online Technical Appendix Table 1) had support and were simulated, both with and without vaccination. For each model, we calculated the yearly numbers of avoided health outcomes resulting from incidence difference with and without vaccination implemented (online Technical Appendix Table 2).

In the economic analysis, we took a weighted average of the incidence differences using Akaike weights (online Technical Appendix). We modeled several different scenarios to account for uncertainty in the calibration process, in vaccine efficacy and vaccine uptake (Table 2). In each scenario, we calculated a weighted model as described above. We analyzed a base case (most likely), best-case, and worst-case scenario to account for uncertainty instead of adopting a probabilistic approach because data on vaccine efficacy and rotavirus-associated health outcomes in Kazakhstan are lacking or sparse. In the base case, we used mean estimates for both vaccine efficacy and calibration values. The best-case scenario was based on the highest vaccine efficacy (86% against severe RVGE and 64% against mild RVGE), in combination with the upper bounds of estimated health outcomes (more events to prevent). The worst-case scenario incorporated the lowest vaccine efficacy (72% against severe RVGE and 51% against mild RVGE) and lower estimates of health outcomes (fewer events to prevent). Vaccine coverage was set to 90% in the base case. Scenarios A and B were constructed as described above, by using coverage of 80% and 100%, respectively (online Technical Appendix Tables 3, 4). Finally, in Scenario C we extended the vaccine protection period to 2 years in line with data from industrialized settings demonstrating high vaccine efficacy through 3 years of life (*32*,*33*). To estimate indirect or herd protection, we compared predictions of the dynamic model with those of a static cohort model, as was previously suggested (*8*) (online Technical Appendix).

Economic Parameters and Cost-effectiveness Analysis

Direct and indirect costs associated with rotavirus disease were recently estimated in a cost-of-illness study

Table 2. Description of scenarios for the economic evaluation of rotavirus vaccination, Kazakhstan

	Vaccine parameters				Children <5 y of age, calibration to 2009 sentinel data			
Scenario	Mean duration of protection, mo	Coverage	Efficacy against severe RVGE	Efficacy against mild RVGE	Deaths	Hospital admissions	Outpatient clinic visits*	Homecare episodes*
Base case	12	0.9	0.80	0.58	68	4,007	I_s-0.2I_h	I_m
Base case, low	12	0.9	0.74	0.51	63	3,740	0.6	0.5I_m
Base case, high	12	0.9	0.86	0.64	74	4,274	1.4	1.5I_m
Scenario A	12	0.89	0.80	0.58	68	4,007	I_s-0.2I_h	I_m
Scenario A, low	12	0.89	0.74	0.51	63	3,740	0.6	0.5I_m
Scenario A, high	12	0.89	0.86	0.64	74	4,274	1.4(	1.5I_m
Scenario B	12	1.0	0.80	0.58	68	4,007	I_s-0.2I_h	I_m
Scenario B, low	12	1.0	0.74	0.51	63	3,740	0.6	0.5I_m
Scenario B, high	12	1.0	0.86	0.64	74	4,274	1.4	1.5I_m
Scenario C	24	0.9	0.80	0.58	68	4,007	I_s-0.2I_h	I_m
Scenario C, low	24	0.9	0.74	0.51	63	3,740	0.6	0.5I_m
Scenario C, high	24	0.9	0.86	0.64	74	4,274	1.4	1.5I_m

*RVGE, rotavirus gastroenteritis; I_s, modeled incidence of severe RVGE; I_h, modeled incidence of hospital admissions; I_m, modeled incidence of mild RVGE.
†The numbers of outpatient clinic and homecare visits were not calibrated.

of RVGE in Kazakhstan (*8*). These costs included direct health care and non–health care costs and indirect costs associated with productivity losses due to the work absenteeism of caregivers and rotavirus-related deaths. For this analysis, cost estimates in 2009 US dollars were inflated to 2012 values by using the consumer price index (Table 3). In the absence of a market price for the rotavirus vaccine in Kazakhstan, we used the 2010 price of pneumococcal vaccine (US $43.00 per dose) purchased by the government. Because the vaccine price is a key determinant of cost-effectiveness, we performed various sensitivity analyses with the price ranging from US $1.00 (assuming program price for traditional Expanded Programme on Immunization vaccines) to US $60.00 per dose (considering a price of pneumococcal vaccine that was the most recent vaccine introduced in the program in Kazakhstan). The program costs included the costs of vaccine doses needed to vaccinate the yearly birth cohorts with 2 doses, a 10% vaccine wastage, and an additional US $267,300 to cover the costs of upgrading the cold chain for rotavirus vaccine in the first year of introduction. A 10% loss from vaccine waste was based on published estimates (*36,37*). The yearly costs of maintaining the cold chain and the costs of training health personnel were estimated in consultation with the Kazakh Ministry of Health. We assumed that rotavirus vaccination does not incur additional costs to parents because it will be administered concomitantly with other vaccines included in the national immunization program.

We assessed the aggregated long-term effect of rotavirus vaccination over a 20-year horizon. All costs and health outcomes were discounted at a rate of 3.0% per year. We conducted cost-effectiveness analyses from the health care system's perspective (including only direct medical costs) and the societal perspective (including indirect costs) using life-years gained as a measure of benefit. We estimated a break-even price for the rotavirus vaccine, in which the total health care costs of the vaccination program were equal to the expected cost savings for the health care system. All results are expressed as mean values with a range to represent realistic vaccination outcomes given the uncertainty in the epidemiologic model. Lacking actual data on uncertainty in the parameter values, we could not express uncertainty in terms of statistical distributions, so we chose to use 1-way sensitivity analyses.

Results

Base Case

Our model projects that the introduction in Kazakhstan of routine rotavirus immunization with 90% coverage and a mean duration of vaccine-induced protection of 1 year would reduce the incidence of severe and mild RVGE in

Table 3. Estimates of projected direct and indirect costs associated with rotavirus disease and rotavirus vaccination, Kazakhstan*

	Cost estimates in 2012 US dollars			
Item (per case)	Direct	Indirect	Total	Reference/source
Rotavirus death	543.33	67,254.13	67,799.46	(*8*)
Severe case (inpatient care)	364.36	181.47	545.83	(*8*)
Moderate case (outpatient care)	32.43	65.57	98.00	(*8*)
Mild case (homecare)	3.49	21.86	25.35	(*8*)
Cost of vaccine per dose, base case	43.00	0	43.00	Authors' assumption
Cold chain upgrade (total first year)	237,300	0	237,300	KMoH
Training costs (first year)	120,096	0	120,096	KMoH
Annual cost of cold chain and training	22,037.74	0	22,037.74	KMoH

*KMoH, Kazakh Ministry of Health.

children <5 years of age within the first year (Figure 1, panels A, B). After ≈4 years of administration of the vaccine program, the dynamics of rotavirus would stabilize, and infection would occur with yearly oscillations. Before the start of the vaccination, the peak incidence of RVGE would be among children <12 months of age. The highest incidence of severe and mild disease postvaccination is found during the second and third years of life, respectively (Figure 1, panels C, D). The age shift is predicted to occur within 3 years of vaccination. The yearly peak is predicted to be delayed by 14–20 weeks compared with the epidemic peak timing without vaccination (online Technical Appendix Figure 4).

During 20 years of vaccination, the predicted incidence of severe RVGE would be reduced by 74% (base case range 64%–80%) of prevaccine levels. The incidence of mild RVGE would be reduced by 56% (range 45%–64%) compared with incidence among unvaccinated children (Figure 1, panels E, F). Our model predicts substantial indirect or herd protection conferred by rotavirus vaccination. The indirect effects account for ≈40% (range 25–33% in relative terms) of the reduction in the projected incidence of severe RVGE, whereas 60% (range 0.28–0.38 in relative terms) of the incidence drop in mild RVGE would be caused by a reduced circulation of rotavirus. Our model projects that over 20 years, a vaccination program with 90% coverage would prevent 881 (range 776–1,004) deaths, 51,891 (range 46,094–57,971) hospital admissions, 370,268 (range 211,825–541,919) outpatient clinic visits, and 1.345 (range 0.641–2.112) million homecare episodes. These values correspond to ≈74% (range 70%–77%) averted deaths, hospitalizations, and outpatient clinic visits and 55% (range 53%–58%) averted homecare episodes compared with the values predicted without vaccination. In that time period, 54,784 (range 48,304–62,442) undiscounted life-years are saved (Table 4).

In the base case, the net undiscounted program costs would be US $530.7 million; the net costs when accounting for cost savings would be US $372.8 (range $325.0–$416.4) million (Table 4). These results would imply a cost of US $23,892 per life-year saved (i.e., incremental cost-effectiveness ratio of US $23,892) in a health care perspective (range $20,557–$27,573) and US $18,044 in a societal perspective ($13,854–$22,779); both estimates were discounted at 3%. Figure 2 shows the cost per life-year gained as a function of the vaccine price per dose in a 20-year perspective. At a cost of US $2.78 (range $2.01–$3.62), the additional cost of the vaccination program would be entirely offset by the cost savings to the health care system corresponding to the medical break-even price.

Scenario Analyses

Varying the vaccination coverage between 80% and 100% (scenarios A and B) did not substantially influence the cost-effectiveness ratio (Table 4). For example,

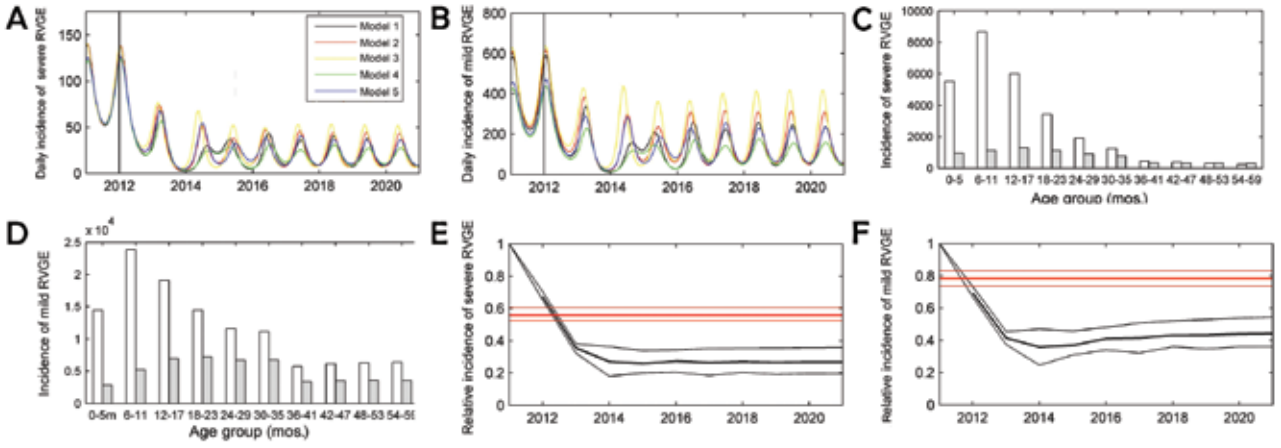

Figure 1. Projected epidemiologic effect of rotavirus vaccination in children <5 years of age in Kazakhstan. A) Estimated daily incidence of severe RVGE (base case scenario) with introduction of rotavirus vaccination in January 2012 in the 5 candidate models. B) Estimated daily incidence of mild RVGE (base case) with introduction of the rotavirus vaccination in January 2012 in the 5 candidate models. C) Yearly age-specific incidence of severe RVGE pre-vaccination (white) and 10 years postvaccination (gray). D) Yearly age-specific incidence of mild RVGE pre-vaccination (white) and 10 years postvaccination (gray). E) Relative incidence of severe RVGE with vaccination compared with the expected incidence without vaccination; the blue curve shows the mean relative incidence with lower and upper bounds predicted by the synthesis of dynamic models, including both direct and indirect effects, while the red curve shows the relative incidence predicted by a static cohort model incorporating only the direct effects (online Technical Appendix, wwwnc.cdc.gov/EID/article/20/1/13-0019-Techapp1.pdf). F) Relative incidence of mild RVGE with vaccination compared with the expected incidence without vaccination; the blue curve shows the mean relative incidence with lower and upper bounds in the synthesis of dynamic models; the red curve shows the relative incidence predicted by a static cohort model.

Table 4. Estimated projected costs in million US dollars and avoided health outcomes of rotavirus vaccination program in Kazakhstan, 2012–2031

Outcome	No vaccination	Base case, 90% vaccine coverage, 1-y vaccination protection			Scenario A, 80% vaccine coverage, 1-y vaccination protection			Scenario B, 100% vaccine coverage, 1-y vaccination protection		
		Mean	Low	High	Mean	Low	High	Mean	Low	High
Avoided outcomes, undiscounted										
Fatal cases	1,310	880	776	1,004	777	681	890	985	876	1 114
In-hospital care	77,205	51,891	46,094	57,971	45,802	40,436	51,447	58,086	52,038	64,396
Out-patient visits	550,896	370,268	211,825	541,919	326,820	185,825	480,935	414,473	239,145	601,983
Home care episodes	2,675,456	1,344,747	640,836	2,112,400	1,163,780	552,160	1,835,487	1,544,096	740,039	2,412,843
Life years gained		54,784	48,304	62,442	48,356	42,375	55,416	61,325	54,534	69,363
Vaccination		530.7	530.7	530.7	471.9	471.9	471.9	589.6	589.6	589.6
In-hospital care	–25.7	–18.9	–16.8	–21.2	–16.7	–14.7	–18.7	–21.2	–18.9	–23.5
Out-hospital care	–16.3	–12.0	–6.9	–17.6	–10.6	–6.0	–15.6	–13.4	–7.8	–19.5
Homecare	–8.5	–4.7	–2.2	–7.4	–4.1	–1.9	–6.4	–5.4	–2.6	–8.4
Indirect costs	–179.4	–122.3	–88.4	–159.7	–107.4	–77.4	–140.9	–137.7	–100.3	–178.9
Total net costs	229.9	372.8	416.4	325.0	333.1	371.8	290.2	411.9	460.1	359.3
Incremental cost-effectiveness ratios, societal perspective										
Discounted 3%	NA	18,044	22,779	13,854	18,280	27,991	13,955	17,775	22,250	13,768
Incremental cost-effectiveness ratios, health care perspective										
Discounted 3%	NA	23,892	27,573	20,557	24,102	23,210	20,620	23,658	27,061	20,526
Threshold prices, 3% discounting										
Medical break-even price†	NA	$2.78	$2.01	$3.62	$2.78	$1.96	$3.60	$2.83	$2.05	$3.65

*Negative values indicate prevented or avoided costs. NA, not applicable.
†The price per vaccine dose at which the vaccinations costs are offset by cost saving generated from lower morbidity and mortality rates.

increasing the coverage to 100% generated only a moderate decrease in the cost per life-year gained (US $23,658 in a health care perspective and US $17,775 in a societal perspective); a marginal change in the cost-effectiveness ratio was also observed when vaccine coverage was decreased to 80%. We included 6 years without vaccination to explore any carryover effects after vaccination is discontinued. The model predicts that such effects are small because infection rates return to prevaccine levels quickly.

Lastly, in scenario C we simulated a 90% vaccine coverage assuming 2-year mean vaccine protection (Table 5; online Technical Appendix Table 5; online Technical Appendix Figure 3). These results suggest a cost of US $22,579 per life-year saved in a health care perspective and US $16,775 in a societal perspective; the medical break-even price was estimated at a cost of US $ 2.95 per dose. Compared with the base case (Table 4), assuming 2 years of vaccination protection reduced the cost per life-year saved by 5.5% in a health care perspective and 7.4% in a societal perspective.

Discussion

Our study evaluated the cost-effectiveness of rotavirus vaccination in a middle-income country by use of a dynamic model. The results indicate that universal rotavirus vaccination in Kazakhstan could prevent 800–1,000 deaths, 46,000–58,000 hospitalizations, 210,000–540,000 outpatient clinic visits, and 0.6–2.1 million homecare episodes during the next 2 decades. Our study suggests that the cost-effectiveness of rotavirus vaccination is determined by 2 key factors: the ability of the vaccines to prevent severe RVGE in children and the market price of the vaccine.

Vaccination also reduces productivity losses because of lower mortality rates and less work absenteeism among parents. However, the small difference between the cost-effectiveness ratios with and without indirect costs is explained by the dominant role of the vaccine costs. In the economic analysis, we calculated the break-even price, representing the price at which the costs of vaccination would be offset by the health care cost savings from avoided cases. With vaccine prices below the break-even price, the vaccination program would become one of

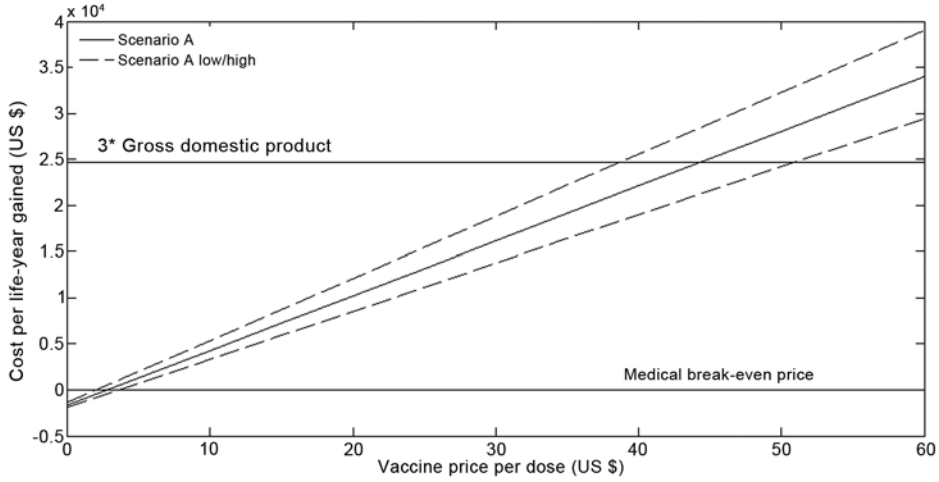

Figure 2. Projected cost (US $) per life-year gained over a 20-year time period (2012–2031) after introduction of rotavirus vaccination in Kazakhstan, according to purchasing price of 1 vaccine dose.

cost saving. We believe that estimating cost per life-year gained and the break-even price of vaccine is informative for decision makers negotiating the price with manufacturers in the absence of an established market price for the product. Whether the cost per life-year represents value for money and is considered cost-effective is a political question for Kazakhstan authorities to decide. WHO has suggested that governments should be willing to pay 3 times gross domestic product per capita per year for a good life-year. For Kazakhstan, this would amount to US $24,660.

A strength of this study is that the results are a synthesis of 5 models and use a likelihood-based approach, in which the models are weighted according to their ability to fit the sentinel data. This approach is common in weather and finance models but not in infectious disease modeling.

Our model demonstrates the role of indirect protection conferred by rotavirus vaccination. In our base case scenario, herd protection accounted for a 40% reduction in the incidence of severe RVGE and a 60% decrease in the incidence of mild RVGE. The contribution of indirect effects to the overall effect of vaccine is an observation also reported by other dynamic modeling studies and supported by empirical data from countries already using rotavirus vaccine in routine immunization programs (*2*,*3*). The incidence reduction in our model is larger than that found by Atkins et al. in a study from England and Wales, where 25% and 40% of the incidence reduction in severe and mild RVGE, respectively, were accounted for by herd protection, assuming a 1-year mean vaccine protection (*38*). This difference may be attributed to differences in assumptions on vaccine-related parameters, the magnitude of the disease burden, population dynamics and other model characteristics. This model has previously been fitted to data from England and Wales with a basic reproductive number of the primary infection of R_0 = 17.6 (*15*), which is smaller than the value estimated for Kazakhstan of R_0 = 19.2 – 2104, thereby suggesting higher transmission pressure in the latter setting.

Data from Finland suggest that vaccine protection may last for >1 year (*39*). We have also tested the model assuming 2 years of vaccine-derived protection. In this case, we found less indirect protection against severe RVGE, roughly representing 20% of the reduction (Table 5; online Technical Appendix Figure 3). The direct effect from vaccination increases because it is calculated from the expected infections in vaccinated children 2–28 months of age, had they not been vaccinated, versus children 2–16 months of age in the base case. We obtained a modest effect from extending the vaccine protection period by 1 year, which may be related to our use of a mean value for the vaccine duration instead of a fixed duration of vaccine protection, implying that some children will experience a shorter duration of protection.

We decided to provide a conservative estimate of the cost-effectiveness of rotavirus vaccination. First, we assumed that direct vaccine-derived protection lasts for 1 year because data on a longer duration of vaccine protection from industrialized countries may not be directly generalizable to Kazakhstan. Second, we assumed that the risk for severe RVGE is age-independent. Vaccination increases the average age of infection, and it is plausible that this risk for severe RVGE is lower for older versus younger children. Third, we applied a lower estimate of vaccine efficacy in our model because Kazakhstan is a developing nation. However, if rotavirus vaccines demonstrate a better efficacy in this country, it may substantially influence the cost-effectiveness of vaccination.

Several limitations in our study warrant care in interpretation of the results. First, our model was fitted to the 2-year sentinel hospital data on rotavirus surveillance on the basis of information from 2 hospitals; hence, changes in annual RVGE incidence and seasonality may have not

Table 5. Estimated projected costs in US dollars and avoided health outcomes from rotavirus vaccination with 2-year protection, Kazakhstan, 2012–2031*

Outcome	No vaccination	Scenario C, 90% vaccine coverage, 2-y vaccination protection		
		Mean	Low	High
		Avoided outcomes, undiscounted		
Deaths	1,310	919	823	1,034
Hospital admissions	77,205	54,163	48,823	59,701
Out-patient visits	550,896	386,479	224,410	558,096
Home care episodes	2,675,456	1,544,202	747,494	2,390,646
Life-years gained	NA	57,183	51,174	64,306
		Avoided costs, undiscounted, US $43 per vaccine dose		
Vaccination	NA	530.7	530.7	530.7
Prevented in-hospital care	25.7	19.7	17.8	21.8
Prevented outpatient care	16.3	12.5	7.3	18.1
Prevented homecare	8.5	5.4	2.6	8.4
Avoided indirect costs	179.4	130.7	95.2	169.2
Total net costs in US$	229.9	362.4	407.8	313.4
		Incremental cost-effectiveness ratios, societal perspective		
Discounted 3%	NA	16,775	21,031	12,952
		Incremental cost-effectiveness ratios, health care perspective		
Discounted 3%	NA	22:759	25:898	19:841
		Threshold prices, 3% discounting		
Medical break-even price†	NA	$2.95	$2.15	$3.79

*NA, not applicable.
†The price per vaccine dose at which the vaccinations costs are offset by cost saving generated from lower morbidity and mortality rates.

been fully captured. Likewise, local data on outpatient visits are sparse. We have attempted to compensate for this by using wide upper and lower confidence bounds on these estimates. Second, the parameters used to characterize natural rotavirus infections were based on those in a study conducted in Mexico and may not properly represent the epidemiology of rotavirus infections in Central Asia. Third, we used continuous aging in the model, which may have introduced a bias arising from persons aging at different rates. Even so, we used a small age band of 1 month, and we tested the model performance without finding severe bias (*14*). Fourth, the choice of simulation period may imply that carryover effects beyond 20 years were disregarded, but the scenario analysis indicates that such effects are small and will not influence the ICERs because of discounting. Fifth, we tested the uncertainty of the vaccine price in the sensitivity analysis, but because of lack of data, we were unable to test the uncertainty of other cost parameters in the model. Finally, because of lack of data, we disregarded improved quality of life in the economic analysis.

In conclusion, rotavirus vaccination in Kazakhstan will provide considerable direct health benefits in terms of reduced illness and deaths. Using the WHO criterion for cost-effectiveness, vaccination would be considered cost-effective under most of the assumptions of our analyses. With a low vaccine price, the avoided disease costs from vaccination will be greater than the vaccination costs. Further study is warranted to measure the benefits of herd immunity conferred by vaccination and to add that information to the current comparison of the costs of illness to those of a national vaccine program.

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Dynamic Modeling of Cost-effectiveness of Rotavirus Vaccination in Kazakhstan

Technical Appendix

Dynamic Model Description and Usage

1. Transmission Dynamic Model

We adapted our previously published dynamic model for rotavirus (*1*,*2*) to Kazakhstan. Rotavirus infection dynamics is complex because both symptomatic and asymptomatic re-infections occur. The susceptibility to new infections and disease severity tend to decline after the first infection (*3*,*4*). In our model, natural rotavirus infection is grouped into three infection types with distinct epidemiological characteristics: primary, secondary and later infections. All infections following a common Susceptible-Exposed-Infected-Recovered (SEIR) structure (Technical Appendix Figure 1). For each infection type, we distinguish between cases of severe rotavirus gastroenteritis (RVGE), mild RVGE and asymptomatic infection using published data on natural history (*3*). The first infection may cause severe RVGE, mild RVGE, or be asymptomatic. The second infection has similar outcomes, but with a lower probability for severe RVGE. Subsequent infections are assumed to cause age-independent proportions of mild and asymptomatic cases. Children are assumed to be protected against RVGE at birth by maternal antibodies for an average of 70 days; the mean protection duration was estimated based on the average period of exclusive breastfeeding in Kazakhstan (*5*).

We modeled the population using monthly age groups for 0-4 years and 10-yearly age groups for 5-14 years, 15-24 years, 25-34 years and 35-44 years; the remaining population above 45 years of age was modeled as one group. We considered age-specific mortality for children <1 year and 1-4 years of age, whereas deaths in those above five years of age were assumed to occur only in the oldest age group (text Table 1). We fitted

the model to the weekly, age-stratified RVGE hospitalizations in children <5 years of age collected from two sentinel hospitals in Kazakhstan from 2007-2009 (*6,7*).

2. Model Fitting and Model Selection

We fitted the model output of severe rotavirus gastroenteritis (RVGE) in children < 5 years old to hospital sentinel data from Kazakhstan, assuming that the pediatric hospitalizations represented a time-independent proportion p of the modeled severe infections. The sentinel study was conducted during 113 weeks from week 44 in 2007 through week 52 in 2009, and included a total of 1,012 children hospitalized with rotavirus-associated gastroenteritis.

We utilized a maximum likelihood approach, assuming that the hospital admissions $h(a,t)$ in age group a and at time point t were Poisson-distributed, with a mean equal to the corresponding incidence of severe infections $s(a,t;\theta)$ predicted by the model. The likelihood function was given by:

$$L(\theta) = \sum_{t=1}^{113}\sum_{a=1}^{60} h(a,t)\log s(a,t;\theta) - s(a,t;\theta) - \sum_{j=1}^{s(a,t;\theta)} \log j \quad (1.1)$$

The parameters to be fitted, $\theta = \{p, \beta 0, \beta 1, \varphi, a_{0-7}, a_{8-23}, a_{24-35}\}$, included the proportion of severe RVGE cases represented in the sentinel hospitalization data (p), an infectivity parameter $(\beta 0)$ and seasonal forcing $\beta 1$ and phase φ described by:

$$\beta 0(1 + \beta 1(\sin(2\pi t / 365 + \varphi))) \quad (1.2)$$

We assumed that children <3 years of age had a higher risk of acquiring infection because rotavirus has a fecal-oral transmission route, and young children have a tendency to put fingers and objects in the mouth. This effect was implemented by fitting parameters for higher transmission to 0-7-month-old children, 8-23-month-old children and 2-year-old children $(a_{0-7}, a_{8-23}, a_{24-35})$. In the preliminary analyses we also tested other assumptions for mixing in the population, including homogeneous mixing and assortative mixing. However, we obtained the best fit by incorporating elevated

transmission to the youngest age groups, and we employed this model structure to make predictions.

To account for uncertainty in the duration of complete immunity following infection, we fitted the model by varying this time period from 6 to 12 months, and we varied the infectiousness in "later" infections relative to that of the primary infection between 1/5 – 1/10. All models were scored using the Akaike Information Criterion (Technical Appendix Table 1):

$$AIC = 2k - 2\ln L(\hat{\theta}) \quad (1.3)$$

where k is the number of fitted model parameters and $L(\hat{\theta})$ is the maximized likelihood.

Five of the candidate models had support $(AIC_j - \min AIC < 5)$, and they were all used to make predictions according to their Akaike weights:

$$w_i = \frac{\exp(-\Delta_i / 2)}{\sum_j \exp(-\Delta_j / 2)}; \qquad \Delta_i = AIC_i - \min AIC \quad (1.4)$$

The fitted models reproduced well the age distribution of pediatric hospitalizations in the sentinel data (Technical Appendix Figure 2, panel A), although with a slight tendency to both over- and underestimate cases in children < 1 year, and 1-year old children, respectively. The models predicted a seasonal peak in late January (week 4). The bi-modal seasonal pattern indicated in the sentinel data (Technical Appendix Figure 2, panel B), which may relate to climatic differences between the central and south region of Kazakhstan where the sentinel hospitals are situated, were not reproduced in the models because seasonal forcing was incorporated using a simple sinusoidal forcing function.

3. Model Calibration

We calibrated the number of deaths and hospital admissions from the incidence of severe RVGE in the model $s(a,t)$ with the use of published estimates for Kazakhstan in 2009 of 68 (63-74) deaths and 4007 (3740-4272) hospital admissions attributable to rotavirus in children < 5 years old. We assumed that age- and time-independent proportions p_d, p_h of

young children with severe RVGE die and become admitted to a hospital, respectively. All children <5 years of age with severe RVGE were assumed to seek outpatient medical care or be hospitalized or both, and based on local data, we assumed that 80% of hospitalized children sought medical care prior to admission (*8*). Lastly, we estimated the number of homecare episodes from the predicted incidence of mild infections $m(a,t)$:

$$
\begin{aligned}
&deaths(a,t) = p_d s(a,t); \quad p_d = \frac{68}{\sum_{2009}\sum_{<5y} s(a,t)}; \quad low / high\,(63/74)\\
&hosp(a,t) = p_h s(a,t); \quad p_h = \frac{4007}{\sum_{2009}\sum_{<5y} s(a,t)}; \quad low / high\,(3764/4267)\\
&outp(a,t) = s(a,t) - (1-0.8)\ hosp(a,t); \quad low / high\,(-/+40\%)\\
&home(a,t) = m(a,t); \quad low / high\,(-/+50\%)
\end{aligned}
\tag{1.5}
$$

Because outpatient clinic visits and homecare episodes were not calibrated, we used their values to validate the models. In the reference year 2009, the models predicted between 28,592-30,189 outpatient clinic visits and 105,850-133,074 homecare episodes using the mean calibration values. The values are consistent with published estimates for Kazakhstan in that year of 32,500 (18,700-42,700) outpatient clinic visits and 130,000 (56,100-213,700) homecare episodes (*9*).

For all five candidate models $j = 1..5$, and

all scenarios *S*, we annually subtracted the number of predicted health outcome events $E_{Sj}^{V}(y)$, with vaccination implemented from the number of events predicted by the model without intervention $E_{Sj}^{0}(y)$. The estimation of yearly avoided health outcomes was calculated as follows:

$$\Delta E_S^V(y) = \sum_j w_j (E_{Sj}^0(y) - E_{Sj}^V(y)) \tag{1.6}$$

where w_j represents the Akaike weights for the candidate models and y is the years from 2012-2031. Tables 2–4 present the predicted incremental number of avoided health

outcomes from 2012-2031 in the base case (Scenario A) and the sensitivity analyses (Scenario B-C).

4. Direct Effects

We used the method suggested by Atkins et al. (*10,11*) to estimate the direct effects of vaccination. In this approach, the direct effects are estimated from the long-term annual number of vaccinated children who would have been infected had vaccination not been implemented. This number is calculated as follows:

$$\Delta I_X^{direct} = \sum_{a=2m}^{16m} \left(\phi VE_X \sum_{j'} \delta I_X^{novacc}(j') \right) \quad (1.7)$$

where ϕ is the vaccine coverage, $VE_X \quad X = \{mild, sev\}$ is the vaccine efficacy and δI_X^{novacc} denotes the incidence in the absence of vaccination at day j'. The expression is summed over all age groups between 2 to 16 months of age, assuming that vaccination is effective from the first dose and that vaccination protects against infection for a mean duration of 12 months following the last vaccine dose scheduled at 4 months of age. This way of calculating the direct effects is identical to the vaccine effect predicted by a static cohort model (*10,11*).

5. Vaccine efficacy

Vaccine efficacy against any infection was calculated as:

$$sero(1 - sus_v) = 0.96(1 - 0.62) = 0.3648 \quad (1.8)$$

where $sero$ is the sero-conversion rate and sus_v is the relative susceptibility against infection in vaccinated children (Technical Appendix Table 1).

Vaccine efficacy against RVGE infection was calculated as:

$$sero(1 - sus_v(prop_{RVGE\_V} / prop_{RVGE\_1})) =$$
$$0.96(1 - 0.62(0.30 / 0.47)) = 0.58 \quad (1.9)$$

here $prop_{RVGE\_V}$ is the proportion of RVGE infections experienced in vaccinated children during their first infection following immunization and $prop_{RVGE\_1}$ is the proportion of RVGE infections in primary natural infection. The numbers correspond to the base case assumption (Technical Appendix Table 1).

Vaccine efficacy against severe RVGE infection was calculated as:

$$sero(1 - sus_v((prop_{sev\_V} prop_{RVGE\_V}) / (prop_{sev\_1} prop_{RVGE\_1}))) =$$
$$0.96(1 - 0.62((0.1175 * 0.30) / (0.28 * 0.47))) = 0.80 \qquad (1.10)$$

where $prop_{sev\_V}$ is the proportion of severe RVGE infections in vaccinated children during their first infection following immunization, and $prop_{sev\_1}$ is the proportion of severe RVGE infections during primary natural infection. The numbers correspond to base case assumption (Technical Appendix Table 1).

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Technical Appendix Table 1. Fitted model parameters and model fit

	Model		Transmission			Relative susceptibility			Fit	
j	inf_{later}	*duration imm.*	β0	β1	φ	a_0–11m	a_12–23m	a_24–35m	AIC	Weight (w)
1	1/10	6m	2.60514	0.03399	0.04981	1.28758	2.43732	2.11278	3854.28750	0.3683
2	1/7	6m	2.55604	0.03124	0.12781	1.07736	2.06568	1.88822	3854.39829	0.3480
3	1/5	6m	2.12452	0.04565	0.25094	1.10342	2.13370	1.93065	3855.00434	0.2574
4	1/7	12m	1.99394	0.02614	0.00034	2.02571	3.97314	3.22687	3860.86022	0.0138
5	1/5	12m	1.88881	0.02483	0.01098	1.47222	2.99835	2.76524	3861.10907	0.0122

Technical Appendix Table 2. Predicted incremental avoided health outcomes from 2012–2031 for base case scenario with 90% vaccination coverage and a mean duration of 1 year of complete vaccine protection

Year	Cumulative avoided deaths			Cumulative avoided hospitalizations			Cumulative avoided outpatient visits			Cumulative avoided homecare episode.		
	Base case	Low	High	Base case	Low	High	Base case	Low	High	Base case	Low	High
2012	23	22	26	1 378	1 282	1 475	9,835	5 893	13 787	41 375	20 633	62 227
2013	68	62	75	3 999	3 693	4 309	28,532	16 972	40 279	121 303	60 195	183 332
2014	120	110	133	7 092	6 507	7 690	50,602	29 903	71 884	208 827	102 882	317 868
2015	170	154	189	10 023	9 135	10 938	71,520	41 978	102 253	292 966	143 497	448 471
2016	218	196	244	12 861	11 648	14 117	91,769	53 527	131 970	370 429	180 415	570 145
2017	267	239	300	15 749	14 213	17 345	112 380	65 314	162 145	446 319	216 488	689 636
2018	314	280	354	18 496	16 630	20 439	131 980	76 424	191 065	518 702	250 770	803 977
2019	360	321	407	21 235	19 051	23 513	151 526	87 550	219 800	589 081	284 091	915 189
2020	405	360	459	23 882	21 385	26 488	170 407	98 275	247 610	656 973	316 210	1 022 548
2021	449	399	509	26 465	23 664	29 392	188 844	108 750	274 758	722 664	347 269	1 126 479
2022	492	437	558	29 013	25 914	32 252	207 022	119 090	301 501	786 791	377 589	1 227 939
2023	535	474	607	31 504	28 113	35 052	224 797	129 192	327 668	849 096	407 028	1 326 574
2024	577	511	655	33 990	30 309	37 842	242 534	139 283	353 752	910 631	436 106	1 423 980
2025	620	548	704	36 507	32 533	40 668	260 498	149 505	380 172	972 596	465 398	1 522 036
2026	663	586	754	39 071	34 797	43 547	278 794	159 911	407 087	1 035 200	494 982	1 621 131
2027	707	624	804	41 641	37 064	46 435	297 128	170 328	434 085	1 097 525	524 395	1 719 905
2028	750	662	854	44 198	39 318	49 312	315 375	180 685	460 975	1 159 417	553 571	1 818 091
2029	794	700	904	46 761	41 577	52 196	333 666	191 066	487 936	1 221 385	582 769	1 916 435
2030	837	738	954	49 327	43 836	55 084	351 972	201 450	514 931	1 283 226	611 889	2 014 639
2031	881	776	1 004	51 891	46 094	57 971	370 268	211 825	541 919	1 344 748	640 836	2 112 400

Technical Appendix Table 3. Predicted incremental avoided health outcomes from 2012–2031 for scenario A with 80% vaccination coverage and a mean duration of 1 y of complete vaccine protection

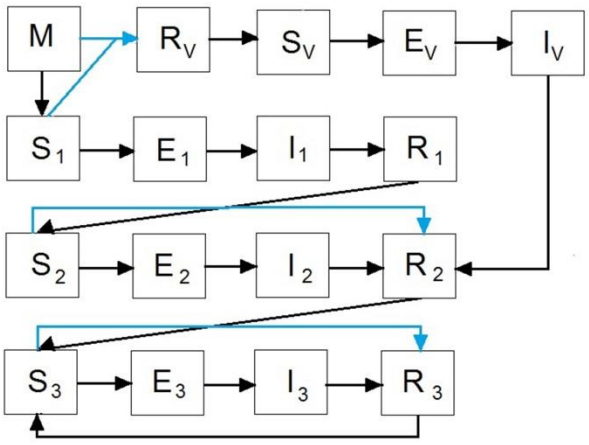
Year	Cumulative avoided deaths			Cumulative avoided hospitalizations			Cumulative avoided outpatient visits			Cumulative avoided homecare episodes		
	A	Low	High	A	Low	High	A	Low	High	A	Low	High
2012	21	20	23	1 260	1 172	1 349	8 992	5 386	12 611	37 525	18 707	56 456
2013	62	57	68	3 647	3 366	3 934	26 026	15 468	36 773	110 791	54 952	167 527
2014	104	94	115	6 100	5 557	6 660	43 529	25 538	62 258	181 271	89 048	276 704
2015	149	133	166	8 753	7 923	9 613	62 456	36 408	89 862	253 166	123 520	389 002
2016	192	171	216	11 304	10 175	12 479	80 661	46 758	116 656	321 512	156 018	496 581
2017	234	208	264	13 764	12 327	15 263	98 213	56 650	142 684	386 269	186 605	599 128
2018	275	244	312	16 220	14 481	18 037	115 735	66 550	168 613	448 830	216 101	698 362
2019	316	280	360	18 639	16 605	20 768	132 997	76 310	194 139	509 634	244 754	794 852
2020	356	314	405	20 972	18 650	23 406	149 648	85 707	218 804	568 155	272 300	887 813
2021	395	348	450	23 256	20 653	25 987	165 946	94 911	242 932	624 857	298 978	977 920
2022	433	381	494	25 511	22 632	28 532	182 034	104 007	266 724	680 234	325 032	1 065 925
2023	470	414	537	27 719	24 570	31 026	197 792	112 913	290 033	734 079	350 350	1 151 537
2024	508	446	580	29 919	26 502	33 508	213 488	121 791	313 239	787 315	375 388	1 236 169
2025	546	480	624	32 157	28 469	36 031	229 453	130 829	336 823	841 092	400 697	1 321 605
2026	584	513	668	34 435	30 471	38 601	245 710	140 029	360 845	895 513	426 306	1 408 072
2027	623	547	713	36 714	32 471	41 174	261 972	149 220	384 899	949 602	451 723	1 494 124
2028	662	580	757	38 981	34 459	43 736	278 150	158 357	408 849	1 003 232	476 893	1 579 540
2029	700	614	802	41 254	36 452	46 305	294 371	167 516	432 865	1 056 932	502 085	1 665 097
2030	739	648	846	43 530	38 446	48 877	310 605	176 678	456 910	1 110 513	527 206	1 750 513
2031	777	681	891	45 802	40 436	51 447	326 820	185 826	480 936	1 163 780	552 160	1 835 487

Technical Appendix Table 4. Predicted incremental avoided health outcomes from 2012–2031 for scenario B with 100% vaccination coverage and a mean duration of 1 y of complete vaccine protection

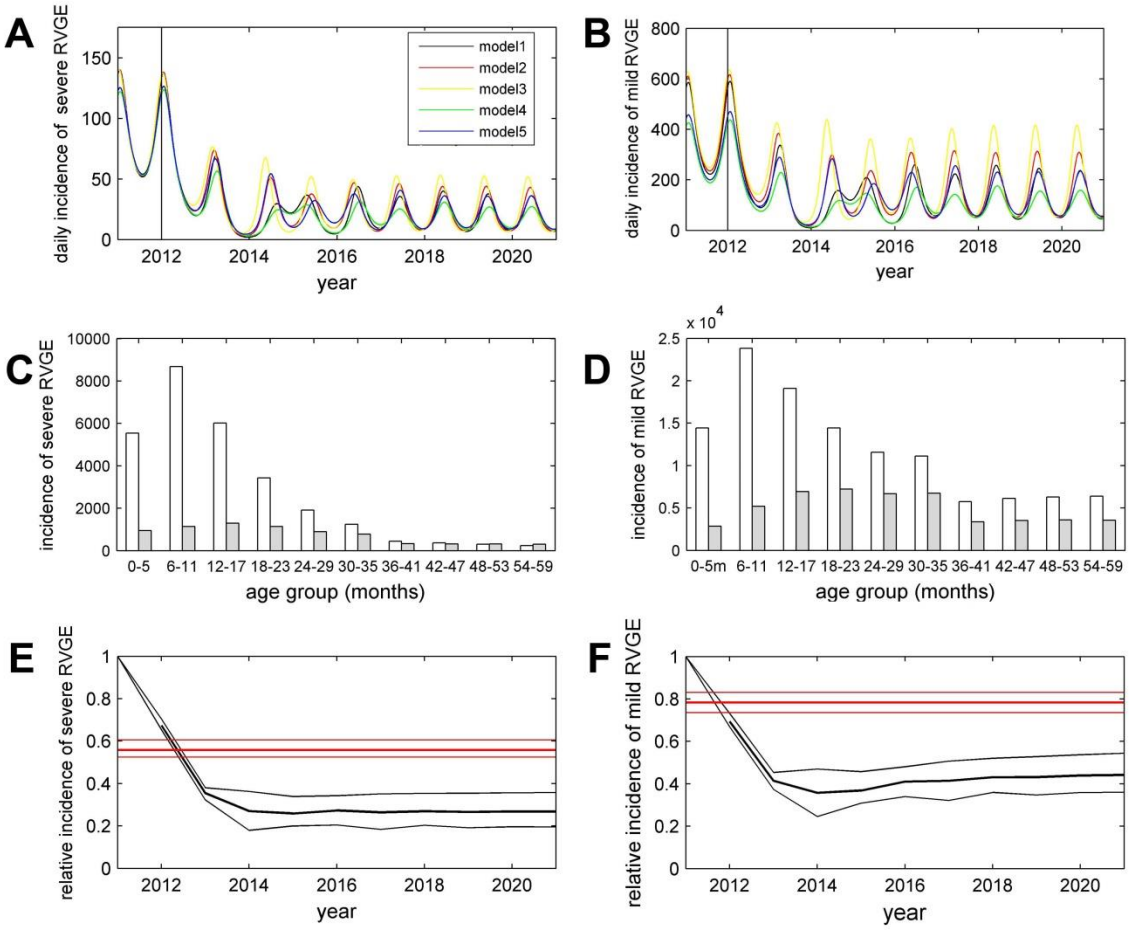
Year	Cumulative avoided deaths			Cumulative avoided hospitalizations			Cumulative avoided outpatient visits			Cumulative avoided homecare episodes		
	B	low	high	B	low	high	B	low	high	B	low	high
2012	25	23	27	1 483	1 380	1 587	10 584	6 344	14 831	44 897	22 396	67 506
2013	74	68	82	4 375	4 046	4 708	31 216	18 594	44 011	132 145	65 615	199 599
2014	138	127	151	8 135	7 544	8 732	58 049	34 669	81 631	245 562	121 722	371 542
2015	194	177	214	11 437	10 534	12 358	81 611	48 407	115 525	335 603	165 107	511 547
2016	249	226	276	14 655	13 422	15 918	104 571	61 683	148 808	430 422	210 951	658 502
2017	304	275	338	17 900	16 339	19 505	127 723	75 086	182 333	514 074	250 707	790 236
2018	355	321	397	20 941	19 028	22 916	149 425	87 446	214 223	599 331	291 471	923 755
2019	408	367	456	24 043	21 808	26 355	171 561	100 220	246 371	678 732	329 188	1 048 845
2020	457	410	512	26 931	24 357	29 600	192 169	111 933	276 704	757 566	366 769	1 172 645
2021	507	455	569	29 871	26 989	32 861	213 148	124 030	307 191	832 037	402 128	1 290 021
2022	554	496	623	32 639	29 432	35 970	232 893	135 256	336 249	906 334	437 519	1 406 776
2023	602	538	677	35 469	31 966	39 110	253 089	146 901	365 602	976 914	471 005	1 518 094
2024	648	579	730	38 169	34 350	42 141	272 355	157 858	393 945	1 048 124	504 904	1 630 064
2025	696	622	784	41 017	36 900	45 301	292 677	169 574	423 483	1 118 178	538 151	1 740 523
2026	743	663	839	43 809	39 366	48 436	312 599	180 908	452 785	1 190 297	572 461	1 853 986
2027	793	707	894	46 707	41 953	51 660	333 279	192 796	482 923	1 260 999	605 970	1 965 604
2028	840	748	949	49 505	44 422	54 803	353 243	204 142	512 311	1 332 238	639 766	2 077 974
2029	889	792	1 005	52 390	46 992	58 018	373 828	215 952	542 363	1 402 790	673 164	2 189 472
2030	937	833	1 059	55 206	49 477	61 182	393 920	227 374	571 934	1 473 849	706 824	2 301 712
2031	986	877	1 115	58 086	52 039	64 396	414 473	239 146	601 984	1 544 096	740 040	2 412 843

Technical Appendix Table 5. Predicted incremental avoided health outcomes from 2012–2031 for scenario C with 90% vaccination coverage and a mean duration of 2 y of complete vaccine protection

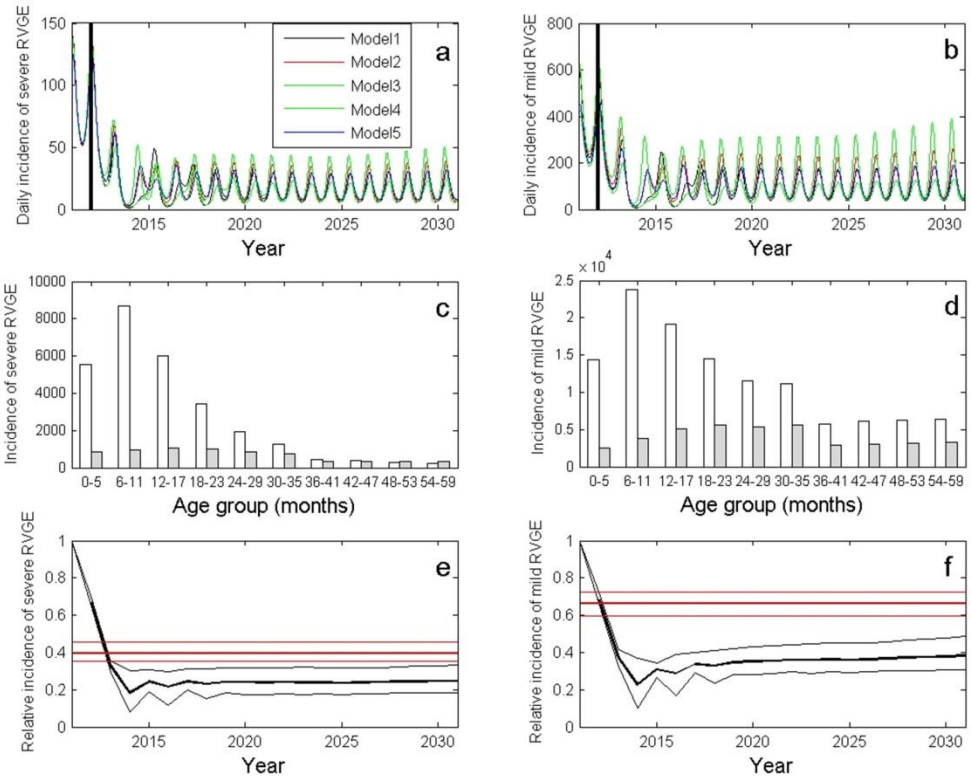
Year	Cumulative avoided deaths			Cumulative avoided hospitalizations			Cumulative avoided outpatient visits			Cumulative avoided homecare episodes		
	C	Low	High	C	Low	High	C	Low	High	C	Low	High
2012	24	22	26	1 407	1 311	1 504	10 042	6 026	14 056	42 593	21 266	63 982
2013	70	65	77	4 149	3 850	4 451	29 605	17 693	41 604	127 686	63 576	192 335
2014	130	120	143	7 679	7 122	8 242	54 793	32 727	77 045	232 402	115 377	351 092
2015	179	164	198	10 552	9 713	11 408	75 295	44 636	106 642	324 443	160 316	492 421
2016	234	214	259	13 798	12 681	14 939	98 454	58 274	139 650	417 173	205 435	635 281
2017	282	256	313	16 618	15 193	18 082	118 578	69 818	169 031	503 492	247 092	769 296
2018	333	301	370	19 605	17 890	21 369	139 890	82 213	199 762	587 580	287 631	899 976
2019	380	343	424	22 398	20 387	24 472	159 824	93 689	228 772	669 164	326 942	1 026 828
2020	427	385	477	25 153	22 857	27 524	179 481	105 040	257 303	747 176	364 468	1 148 316
2021	473	426	528	27 845	25 270	30 507	198 687	116 127	285 184	823 119	401 010	1 266 551
2022	517	465	579	30 463	27 613	33 413	217 372	126 897	312 348	896 776	436 426	1 381 301
2023	561	504	628	33 057	29 938	36 286	235 877	137 582	339 206	968 528	470 920	1 493 105
2024	604	543	677	35 616	32 229	39 124	254 135	148 110	365 739	1 039 316	504 951	1 603 405
2025	649	582	727	38 225	34 569	42 015	272 755	158 863	392 761	1 110 564	539 213	1 714 392
2026	694	622	778	40 876	36 944	44 953	291 668	169 775	420 231	1 182 773	573 940	1 826 869
2027	739	662	829	43 538	39 328	47 906	310 667	180 733	447 834	1 255 041	608 673	1 939 501
2028	784	702	880	46 189	41 701	50 848	329 583	191 637	475 335	1 327 135	643 302	2 051 926
2029	829	742	931	48 845	44 077	53 796	348 533	202 555	502 891	1 399 497	678 050	2 164 797
2030	874	783	983	51 505	46 456	56 749	367 514	213 489	530 501	1 471 926	712 816	2 277 818
2031	919	823	1 034	54 163	48 832	59 701	386 479	224 410	558 096	1 544 203	747 494	2 390 646



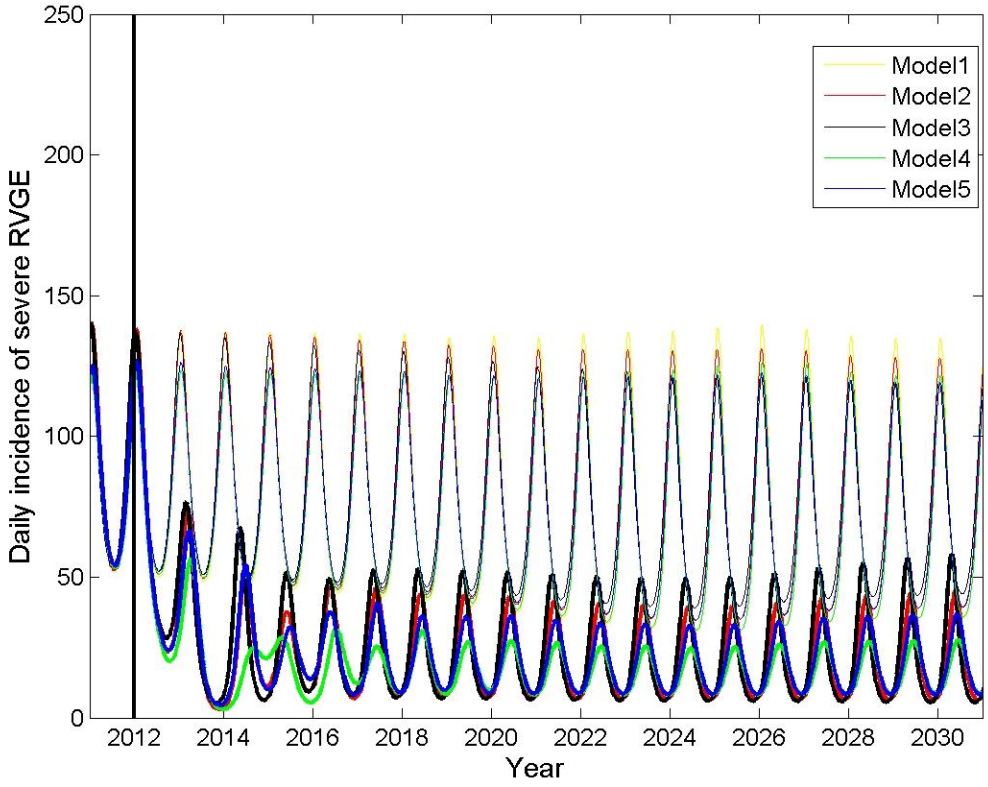
Technical Appendix Figure 1. Model schematics of the SEIR dynamic natural history model. The effect of vaccination is shown with blue arrows.



Technical Appendix Figure 2. Model fitting to sentinel hospitalization data (N = 1013 weeks) from Kazakhstan, 2007–2009; A) Age-specific model in 2-month age groups; B) Weekly incidence of hospitalizations caused by rotavirus (solid line) and fitted incidence of severe infections in the model (dashed line); the total numbers of severe infections in children <5 years were multiplied with a factor $p\_sev = 0.01556$ to yield a similar mean as for the observational data. *GE: gastroenteritis.



Technical Appendix Figure 3. Epidemiologic impact of rotavirus vaccination in children <5 years in Kazakhstan with a 2-year mean vaccine protection. A) Estimated daily incidence of severe RVGE (base case) with introduction of rotavirus vaccination in January 2012 in the five candidate models; B) Estimated daily incidence of mild RVGE (base case) with introduction of the rotavirus vaccination in January 2012 in the five candidate models using a similar color scheme as shown in legend A); C) Yearly age-specific incidence of severe RVGE pre-vaccination (white) and 10 years post-vaccination (gray); Yearly age-specific incidence of mild RVGE pre-vaccination (white) and 10 years post-vaccination (gray); E) Relative incidence of severe RVGE with vaccination compared with the expected incidence without vaccination; the blue curve shows the mean relative incidence with lower and upper bounds predicted by the synthesis of dynamic models, including both direct and indirect effects, while the red curve shows the relative incidence predicted from a static cohort model incorporating only the direct effects (Supplemental Section S.3); F) Relative incidence of mild RVGE with vaccination compared with the expected incidence without vaccination; the blue curve shows the mean relative incidence with lower and upper bounds in the synthesis of dynamic models, while the red curve shows the relative incidence predicted by a static cohort model.



Technical Appendix Figure 4. Epidemiologic effects of rotavirus vaccination in children <5 years in base case model: Estimated daily incidence of severe rotavirus gastroenteritis in the 5 candidate models with introduction of rotavirus vaccination in January 2012 (fat lines) and without vaccination implemented (slim lines).